CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DIPHACINONE

Chemical Code # 000225, Tolerance # 50154
SB 950 # 298

November 17, 1986
Revised December 20, 1993, March 7, 1996

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study on file
Chronic toxicity, dog:	Data gap, no study on file
Oncogenicity, rat:	Data gap, no study on file
Oncogenicity, mouse:	Data gap, no study on file
Reproduction, rat:	Data gap, no study on file
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	Data gap, no study on file

Gene mutation: No data gap, no adverse effect

Chromosome effects: No data gap, no adverse effect

DNA damage: No data gap, no adverse effect

Neurotoxicity: Not required at this time

Toxicology one-liners are attached.

All record numbers through 144121 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T960307.
Prepared by J. Parker, 11/17/86.
Updated by: P. Iyer, 12/20/93; by J. Gee, 3/7/96

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

No study on file.

CHRONIC TOXICITY, RAT

No study on file.

CHRONIC TOXICITY, DOG

No study on file.

ONCOGENICITY, RAT

No study on file.

ONCOGENICITY, MOUSE

No study on file.

REPRODUCTION, RAT

No study on file.

TERATOLOGY, RAT

**047 124649, "An Oral Teratology Study in Rats with Technical Diphacinone", (E.M. Daniel, Springborn Laboratories, Inc., Study No. 3284.3, 5/6/93). Diphacinone, purity >98%, administered by gavage at nominal concentrations of 0 (Mazola* Corn Oil), 0.010, 0.025 or 0.075 mg/kg to 25 mated female Sprague-Dawley rats on days 6 through 15 of gestation. A high dose female was euthanized in-extremis due to severe clinical signs. This high dose female had reduced activity, shallow breathing, pale extremities and eyes, reddish fluid in the cage tray, reddish urogenital staining and reddish vaginal discharge. Hair loss, dark material around the nose and reddish vaginal discharge was observed sporadically in all groups, and a low incidence of reddish urogenital staining and reddish fluid in the cage pan was observed in the mid and surviving high dose females. Actual maternal NOAEL = 0.0195 mg/kg/day (0.025 mg/kg/day nominal dose). The increased early resorption and post-implantation loss for the high dose was not statistically significant and hence equivocal. There was no evidence of teratogenicity. ACCEPTABLE. (J. Kishiyama and P. Iyer, 12/20/93).

047 124648, "An Oral Range-Finding Study in Rats with Technical Diphacinone (EPA-FIFRA)", (E.M. Daniel, Springborn Laboratories, Inc., Study No. 3284.2, 4/20/93). Diphacinone, purity >98%, administered by gavage at concentrations of 0 (Mazola* Corn Oil), 0.010, 0.025, 0.050, 0.075 or 0.100 mg/kg to 6 mated female Sprague-Dawley rats on days 6 through 15 of gestation. Technical diphacinone administered at 0.100 mg/kg/day resulted in the death of two females (one died and the other euthanized in-extremis). Clinical signs of toxicity observed prior to death were reddish colored vaginal discharge, reddish fluid/jelly-like matter on the cage paper, reddish urogenital staining, cool to touch, partially closed eyes, pale colored eyes, dark material around mouth and nose, unkempt appearance, and shallow breathing. Reddish

colored vaginal discharge was also observed for one 0.075 mg/kg female. No test article-related changes were noted in the fetuses. Based on results, 0.010, 0.025 and 0.075 were selected as dose levels for the definitive teratology study in rats with diphacinone. Supplementary (J. Kishiyama and P. Iyer, 12/20/93).

TERATOLOGY, MOUSE

50154 014/015/016/021/022 35373 Teratology Mouse (no date, Bowling Green), Diphacinone, no purity stated, @ 0, 0.1, 0.5, 1.0 or 2.5 mg/kg gavage day 6-13 to 5 female mice/group; maternal toxicity all animals of high dose group, and 1/5 from the 1.0 mg/kg group died. **No teratogenic effect observed**. **Unacceptable**. No individual fetal data, too few animals. Insufficient information for independent assessment of toxicity (C. Aldous, 10/21/85; J. Parker, 11/17/86).

TERATOLOGY, RABBIT

No study on file.

According to statements in the protocols of the following studies in genotoxicity, they were designed to comply with FIFRA Guidelines (40 CFR Part 158) "as amended". Addendum 9, USEPA, March, 1991, Subdivision F, describes the tests which should be in the initial battery. The following three assays conform with this battery. Gee, 1/15/94.

GENE MUTATION

**037 114938, "Ames/Salmonella Plate Incorporation Assay on 2-Diphenylacetyl-1,3-indandione (Diphacinone)", (Leon F. Stankowski, Jr., Pharmakon Research International, Inc., PA. Report # PH 301-HA-001-91, 22 April 1992). Diphacinone (97.4% indicated purity) was tested using

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 at 0 (DMSO), 0.50, 1.67, 5.0, 16.7, 50.0, 167.0, 333.0, or 500.0 µg/plate. The reversion assay was performed in triplicate, with and without activation (Aroclor 1254 induced male Sprague-Dawley rat liver homogenate) and the treatment was for 48-hours. Repeat trial. No increase in reversion rate. Acceptable (H. Green, 10/21/92, and P. Iyer, 12/14/93).

50154 011 33912 Salmonella & Saccharomyces (no date, Litton Bionetics)
Diphacinone, 96.57% purity tested at 1, 10, 100, 500 or 1000 ug/plate with and without activation; TA 1535, TA 1537, TA 1538, TA 98 and TA 100, single plate/strain **Unacceptable.** No cytotoxicity measured, no confirming trial (C. Aldous, 7/19/85).

CHROMOSOME EFFECTS

**039 116245, "AS52/XPRT Mammalian Cell Forward Gene Mutation Assay on 2-Diphenylacetyl-1,3-indandione (Diphacinone)", (Leon F. Stankowski, Jr., Pharmakon Research International, Inc., Waverly, PA. Report # PH 314-HA-001-91, 5/27/1992), diphacinone with indicated purity of 97.4%. The CHO/XPRT assay was performed in duplicate with 5-hour exposure using AS52 Chinese Hamster ovary cells in the presence of activation (Aroclor 1254 induced rat liver homogenate) at concentrations of 0, 0.167, 0.500, 1.67, 5.0, 10.0, 16.7, 33.3, 50.0, 75.0, 100.0, 125.0, 150.0, 175.0, or 200.0 mg/ml, and in the absence of activation at concentrations of 0, 0.0167, 0.0500, 0.167, 0.500, 1.67, 5.0, 7.5, 10.0, 12.5, 15.0, 16.7, 17.5, or 20.0 mg/ml. 2 trials. No increase in frequency of mutation. Acceptable. (H. Green and P. Iyer, 12/6/93).

DNA DAMAGE

**040 116727, "In Vivo Micronucleus Test with Diphacinone in Mouse Bone Marrow Erythropoietic Cells", (Juan R. SanSebastian, Pharmakon Research International, Inc., Waverly, PA. Report #

PH 309-HA-001-91, 30 June 1992). Technical diphacinone (97.4% indicated purity, technical grade) was administered once by gavage to 5 or 8 CD-1 mice per sex per sampling group at 0 (corn oil), 37.5, 75.0, and 150.0 mg/kg. The marrow of the femur was sampled at 24, 48, and 72 hours post-treatment. **No increase in the frequency of micronucleated polychromatic erythrocytes was observed. Acceptable** (H. Green, and P. Iyer, 12/10/93).

NEUROTOXICITY

Not required at this time.

SUBCHRONIC, RAT

50154-056 144121 "A 14-day oral toxicity evaluation of technical diphacinone in young adult Sprague Dawley rats" (Rogers, A. J., Bell Laboratories, Inc., WI, Study number 100-056, 6/1/94) Five per sex per group were given diphacinone, technical grade, Lot no. CL-255, 99.7%, by gavage in a single dose at 0 (corn oil), 0.13, 0.20, 1.0 or 2.5 mg/kg or in 14 doses at 0, 0.025, 0.04, 0.085 or 0.175 mg/kg. The purpose of the study was to determine the NOEL for toxicity, lethality and coagulopathy in the rat. Prothrombin time and partial thromboplastin time were determined at 24 hours, 96 hours and at weekly intervals over 30 days. No histopathology was done. Deaths occurred at 0.175 mg/kg with a NOEL of 0.04 mg/kg, 14 doses, for coagulopathy and 0.085 for signs of toxicity and lethality. For a single dose, 0.13 mg/kg was considered to be the NOEL. Supplemental data. (Gee, 3/4/96)